Intracellular Bacterial Pathogen Therapeutic Target Product Profile Guidelines

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This Target Product Profile Guideline is approved and effective upon following signature:

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2/24/2009

Mr. David Hough **Date**

Director

Transformational Medical Technologies Initiative

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Part I: Purpose and background

One of the primary program product goals of the Transformational Medical Technologies Initiative (TMTI) is stated as follows:

> Two (or more) broad-spectrum countermeasures. One product will apply to viruses (especially hemorrhagic fever viruses). The second product will be active against intracellular bacterial pathogens. Additional products will be developed depending on funding. Each will act against the agents by affecting critical molecular pathways essential to the success of the agent or its effect on the host. The goal is to have at least two investigational new drug (IND) candidates developed within five years that can be used against multiple viruses and bacteria under Emergency Use Authorization (EUA), however, licensure is the ultimate goal and will be pursued throughout the program against multiple viruses and bacteria[1].

To assist in the articulation of TMTI product requirements, and in the evaluation of specific drug candidates, Target Product Profiles (TPPs) are being developed. The stakeholders for TPPs for pharmacologic countermeasures include:

- TMTI Program Management Office
- Joint Requirements Office-Chemical, Biological, Radiological, and Nuclear Defense (JRO-CBRN)
- TMTI Performers

TPP Stakeholders	TPP Function
TMTI Program Management Office (PMO)	Each TPP sets product development strategies for each anti-bacterial therapeutic
Joint Requirements Office-Chemical Biological Defense (JRO-CBRN)	Each TPP serves as a basis for communication of expected product characteristics to the warfighter requirements community
TMTI Performers	Each TPP establishes expected characteristics (requirements) for each anti-bacterial therapeutic

Additional TMTI stakeholders include the Office of Secretary of Defense Special Assistant for Chemical and Biological Defense and Chemical Demilitarization Programs (SA (CBD&CDP)) and the TMTI Executive Office (EO).

The EO is composed of the following organizations:

- Joint Program Executive Office for Chemical Biological Defense (JPEO CBD)
- Joint Science & Technology Office (JSTO) and Defense Threat Reduction Agency's Chemical & Biological Defense Directorate
- TMTI Program Office

TPPs will be referenced when setting evaluation criteria for solicitations and in candidate project selection, highlighting project(s) that demonstrate product attributes desired by

[1] *Medical Biodefense Research, Development, Test & Evaluation Plan*, approved December 27, 2006

TMTI. Finally, the TPPs will be considered when making "go/no-go" decisions at milestone decision points.

Since each TPP may be applied to several countermeasure projects, it is not intended to be the package insert or labeling for a specific drug; however, the TPP is only a guideline. Drug labeling will later be developed for specific products for use in discussion with the FDA, once supporting preclinical data has been generated.

The TMTI program was given broad guidance through the current Initial Capabilities Documents (ICDs) to develop broad-spectrum medical therapeutics to mitigate the negative operational impact of a biological attack. The therapeutic must be safe and effective, easy to use, and cause minimal side-effects. The therapeutic must minimize the logistical burden through:

- Infrequent dosing;
- Ease of administration;
- Minimal post-administration monitoring requirements e.g, therapeutic drug levels, frequent laboratory based toxicity screens;
- Long shelf life;
- Resistance to harsh environmental conditions, e.g. extreme temperatures;

Part II: Criteria targets for an intracellular bacterial pathogen therapeutic

This Target Product Profile guideline describes drug candidates to be used as therapeutics targeted against intracellular bacterial pathogens. The drug candidates will be used to treat patients who have been exposed to the pathogen, are symptomatic, and who have the potential to be hospitalized for medical treatment.

Efficacy

Criterion	Objective	Threshold
% Protected (Survival)	100% survival in pivotal studies is the ideal goal, although likely unattainable.	A statistically and clinically significant increase in survival over untreated controls in pivotal animal model studies

An objective defined as statistically superior to the current standard of care is confounded by the fact that for many of the biowarfare (BW) diseases, there are no medical countermeasures available for comparison. In addition, the genetically modified organism may be resistant to existing countermeasures.

A threshold defined to be statistically non-inferior to the current standard of care is confounded by the possibilities that the genetically modified organism may be resistant to the current standard of care. In many of the BW-related diseases the efficacy of the current standard of care is either not well defined or non-existent.

Safety

Criterion	Objective	Threshold
Side effect profile	No serious adverse effects	Safety data acceptable to the FDA

The preferred level of safety for a therapeutic is no serious adverse effects. However, the threshold is met when safety findings are acceptable to the FDA.

Dosage

Criterion	Objective	Threshold
Duration of therapy	10 days	60 days
Frequency of therapy	Once per week	Once every four hours
Route of administration	Oral or topical, fast disintegrating (no water needed), and either intravenous or intramuscular	Intravenous or intramuscular
Time needed for efficacious treatment	Efficacious (survival benefit expected) when administered in the established disease state	Efficacious (survival benefit expected) when administered during prodrome

Rationale

Duration: Based on current treatments for biological warfare agent related diseases

- Objective: plague
- Threshold: inhalational anthrax

Frequency of therapy: Based on current or late-IND treatments for biological warfare agent related diseases or other serious bacterial diseases.

- Objective: dalbavancin
- Threshold: imipenem or penicillin for life-threatening indications

Route of administration: Based on antibiotics used to treat serious bacterial infections. Both oral and parenteral formulations are listed as objectives for therapeutics, because parenteral treatment may be necessary for treating critically ill patients. Oral therapy will be field-expedient for patients with early illness.

Time needed for efficacious treatment: Defined as the latest time point within the post-symptomatic disease state at which survival is expected upon administration of treatment.

Dosage, formulation, and route of administration are critical elements when generating medical products for the warfighter. The operational requirements of the warfighter to remain active and in the field, dictate the need to carry as little bulk as possible. Also, by aggressively targeting dosage thresholds that minimize the logistical burden (e.g.,

avoiding the need to carry excessive water, numerous treatment courses, or an IV into the field), the developed drug is more likely to meet the warfighter requirements documented by the Joint Requirements Office (JRO) in the relevant ICD.

Patient Population

Criterion	Objective	Threshold
Age	All DoD beneficiaries	18-65
Teratogenicity	Category B	Category D

The category of "All DoD beneficiaries" includes juveniles, the geriatric population and the immunocompromised population. While this would be the objective for developing a drug due to potential off-label uses, the Department of Defense (DoD) is funding development of a drug for the warfighter, the population indicated in the threshold value.

The objectives and thresholds for teratogenicity are derived from the ratings from post-exposure of medications recommended by the U.S. Public Health Service for therapy of BW-agent related bacterial diseases (e.g., inhalational anthrax, plague, etc.).

The FDA provides teratogenicity ratings for all licensed medications.

Category A refers to:

- Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).

Category B refers to:

- Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.

Category C refers to:

- Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Category D refers to:

- Positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

Manufacturing

Criterion	Objective	Threshold
Time to scale	1 month/150,000 treatment courses	1 year/150,000 treatment courses/associated date
Stability: Shelf life at time of licensure	5 years	2 years
Storage	No cold chain	Cold chain

Storage preferences are not recorded as targets, but include the following considerations: minimized bulk, ease of dispensing, and temperature insensitivity.

These values assume that several trade-offs will occur determining the final objective and threshold values for manufacturing. These trade-offs include scalability, time to scale, stability (to determine the amount that can be stockpiled), efficacy, dosing (to determine the number of doses needed per patient) and cost of production (directly correlated with the stated amount DoD will pay).

Part III: Recommendations for TPP usage in portfolio management and downselection

The TPP guideline establishes expected characteristics (requirements) for each relevant drug candidate; while Integrated Medical Technology Readiness Levels (TRLs) are used to measure progression towards those requirements within TMTI-defined phases of drug development. During each Milestone Decision Review, a product candidate will be measured against the TRLs. Though a candidate may have successfully achieved a required TRL, insufficient progress towards meeting TPP objectives, could still result in a negative Milestone Decision.

In the clinical stages, actual data will be used to compare against the objective and threshold values for the TPP. Candidates that do not meet threshold values may be prohibited from advancing to the next milestone.